REMARKS

Claims 1-72 are pending.

Claims 1-4, 7-9, 64, 66 and 67 stand rejected. However, this grouping is inconsistent with the previously made election, as well as the Examiner's notation that claims 1-4, 6-9, and 64 are elected and claims 5, 10-63, 65, 68-72 are withdrawn from consideration. Accordingly, Applicants request reconsideration of the grouping of the elected claims as is detailed below.

Claim 1 is amended. The remaining claims are unchanged.

THE AMENDMENTS

The specification has been amended to correct a typographical error noted by the Examiner and others found by Applicants. Substantively, the disclosure is unchanged and no new matter has been introduced.

Claim 1 was amended to clarify that the chelated complexes of the present invention are synthesized or formed *in situ* in a sample being tested. Support therefor can be found, for example, at page 6, lines 1-10 and claim 57 (synthesizing the complex) and page 6, lines 13-20 and claims 68-70 (forming the complex *in situ*).

THE REQUIREMENT FOR RESTRICTION

In the previous Restriction Requirement, the Examiner placed claims 1-9 and 65-67, drawn to complexes of bacteriocins and metals, in the elected Group I. Applicants asserted that claims 63 and 64 should also have been included. Applicants acknowledge the Examiner's alteration of the restriction requirement so as to include claims 63 and 64 in the elected Group I. *Therefore, claims 1-9 and 63-67 are in the elected group.*

Turning now to the elected species, Applicants previously elected to prosecute a lantibiotic as the bacteriocin species, and a transition metal as the detectable label species. The elected claims read on or do not read on these elected species as follows:

Claim 1: generic claim-*reads on* elected species

Claim 2: generic claim-*reads on* elected species

Claim 3: generic claim-*reads on* elected species

Claim 4: transition metals-*reads on* elected species

Claim 5: lanthanide metals-does not read on elected species

Claim 6: lantibiotics-*reads on* elected species

Claim 7: a transition metal, Co-*reads on* elected species

Claim 8: a lantibiotic, nisin-*reads on* elected species

Claim 9: transition metals, Co and Cr-*reads on* elected species

Claim 63: complex of lantibiotic and lanthanide metal-does not read on elected species

Claim 64: complex of lantibiotic and transition metal-*reads on* elected species

Claim 65: bacteriocin of SEQ ID NO:8, sequence for the lantibiotic nisin (see page 10, lines 15-16 of the Specification)-*reads on* elected species

Claim 66: bacteriocin of SEQ ID NOS: 1-7, sequences for Class A lantibiotics (see Table 1, pages 17-18 of the Specification)-*reads on* elected species

Claim 67: bacteriocin of SEQ ID NOS: 1-7, sequences for Class A lantibiotics (see Table 1, pages 17-18 of the Specification)-*reads on* elected species.

Therefore, while claims 1-9 and 63-67 are in the elected group, Applicants assert that claims 1-4, 6-9 and 64-67 read on the elected species, while claims 5 and 63 do not read on the elected species. Accordingly, claims 1-4, 7-9 and 64-67 should be prosecuted.

In stating that claims 1-4, 7-9, 64, 66 and 67 stand rejected, the Examiner has not included claim 6, which is directed to the elected lantibiotic species and has not included claim 65, which is also directed to the elected lantibiotic species.

Correction is respectfully requested.

OBJECTION TO THE SPECIFICATION

The Examiner has objected to the specification due to certain informalities on page 42, lines 25-26. The error has been corrected as suggested by the Examiner.

REJECTION UNDER 35 U.S.C. §101 (UTILITY)

Claims 1-4 and 7 stand rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. In particular, the Examiner characterizes these claims as reading on chelated complexes of bacteriocins and a metal, including both isolated complexes and complexes in the

natural environment. The Examiner cites Pommer et al, *J. Bio. Chem.* 274(38): 27153-27160 (1999) (hereinafter "Pommer") to support his position.

With respect to the Examiner's contention that claims 1-4 and 7 are directed to non-statutory subject matter, Applicants point out that the MPEP § 2106(IV)(A) recognizes that the expansive language of 35 U.S.C. §101 indicates that patentable subject matter includes "anything under the sun that is made by man." (Internal quotations and citations omitted). While natural phenomena are not patentable, the rejected independent claim, as amended, is clearly not directed to a natural phenomenon *per se*. Rather, claim 1 is generally directed to chelated complexes that are synthesized or formed *in situ* to detect biological analytes. While Pommer discusses natural bacteriocin that contain a single transition metal ion (i.e., zinc or nickel), the transition metal was said to be "not essential" for its activity. The presently claimed chelated complexes require the incorporation of a transition or lanthanide metal in order for the complexes to work for the intended purpose – to detect biological analytes. Accordingly, Applicants assert that claim 1 as amended and claims 2-4 and 7 are patentable under 35 U.S.C. §101, and respectfully request removal of this rejection.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4, 7-9, 64, 66 and 67 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner asserts that while the claims read broadly on the claimed complexes of transition metals with bacteriocin variants, the application does not provide any examples or other written description support for such variants. Applicants respectfully disagree.

The Examiner's attention is respectfully directed to the written description requirements as set forth in The Revised Interim Guidelines for the Examination of Patent Applications (1999) Federal Register 64(244):71427-71440. The first paragraph of section I.A, states "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." The Guidelines further state that "[t]he absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. §112, first paragraph, for lack of adequate written description."

The meaning of the terms "fragments," "homologs," and "variants" of complexes of bacteriocins are well-known and established in the field. Moreover, Applicants define these terms in the specification at page 10, lines 1-24 (emphasis added), as follows:

> The term "fragment" refers to a portion of a bacteriocin that has been enzymatically or chemically truncated or cleaved. Such a fragment may encompass any portion of the native amino acid sequence of the bacteriocin.
>
> The term "variant" refers to a natural or genetically engineered variation in amino acid sequence relative to the native bacteriocin amino acid sequence, such as one, two, three or more amino acid substitutions, deletions, or additions, natural allelic variants, or variations in post-translational processing.
>
> The term "homolog" refers to a bacteriocin having an amino acid sequence homologous to the amino acid sequence of the bacteriocins discussed herein. Such homologous sequences are obtained from natural nucleic acid sequences (e.g., genomic DNA, cDNA), as well as synthetic or mutagenized sequences, by performing hybridization experiments under stringent conditions, wherein the nucleic acid sequences encoding homologs hybridize to DNA sequences encoding the amino acid sequences disclosed herein for a particular bacteriocin. **For example, homologs to nisin are generally peptides whose nucleic acid sequence hybridizes to the nucleic acid sequence for nisin (SEQ ID NO:8) under stringent conditions.** Such homologs would be expected to comprise an amino acid sequence that is approximately 90% to about 99.9%, preferably about 95% to about 99.9% homologous with that of the native amino acid sequence for nisin, and to exhibit similar structural and functional characteristics. Similarly, other bacteriocins will have homologs comprising amino acid sequences that are approximately 90% to about 99.9%, preferably about 95% to about 99.9% homologous with that of their respective native amino acid sequences. All such homologs would also be expected to form similar metal chelates and bind to target pathogens with the same characteristics of the bacteriocins described herein.

The fact that these terms are defined in Applicants' specification, one of skill in the art would have no difficulty understanding the scope of the claimed genus of bacteriocin fragments, homologs and variants thereof. Further, in claiming a complex comprising a bacteriocin and fragments, homologs, and variants thereof, Applicants are not simply outlining a goal, they are reciting a well-known and commonly understood genus. The goal of the invention is to provide a composition comprising a bacteriocin that can be modified using well-known techniques to

produce fragments, homologs, and variants thereof. Examples of such variants are described, for instance, in the specification as follows:

> The present invention thus also includes within its scope **bacteriocin homologs encoded by DNA sequences** capable of hybridizing, preferably under stringent conditions, with the DNA sequences described herein, or sequences which code for the bacteriocin amino acid sequences disclosed herein using the degeneracy of the genetic code and coding for proteins having substantially the same activity. Stringent hybridization conditions select for DNA sequences of greater than 85% or, more preferably, greater than about 90% homology. Page 11, lines 3-9, emphasis added.

> While lantibiotics are the preferred bacteriocins, any of the **generally cationic peptides** synthesized by bacteria, plants, mammals or insects having antimicrobial activity and forming complexes with transition or lanthanide metals could be used. Therefore, diverse species of cationic membrane active peptides such as the non-lanthionine containing bacteriocins, defensins, cecropins, and magainins, for example, are equally useful to generate metal complexes which bind to the membranes of pathogens, and can be used for the detection of pathogenic species. **Fusion proteins, fragments, homologs and variants of these cationic peptides** also are encompassed within the present invention, so long as membrane binding activity is preserved. However, the function of pore formation is not necessary for detection, and therefore, the bacteriocins or other cationic antimicrobial peptides, fusion proteins thereof, fragments, homologs and variants thereof are included even if the pore forming activity has been lost due to changes in amino acid sequence or secondary structure. Page 19, lines 1-13, emphasis added.

> **Engineered variants such as fusion proteins** or constructs comprising the amino acid sequence of one or more bacteriocins may also be utilized in the present invention. A particularly preferred embodiment is a fusion protein comprising multiple copies of a bacteriocin. A preferred bacteriocin for constructing a multimer of bacteriocins is nisin. In some instances, the fusion construct is a multimer of one particular bacteriocin. In other instances, the fusion construct is a multimer of different bacteriocins. Spacer sequences comprising an amino acid sequence of between about 5 to about 25 amino acids, preferably between about 1 to about 10 amino acids, may be included between the C-terminus of one subunit of bacteriocin and the N-terminus of the next bacteriocin. Any of the above variations in bacteriocin structures may be used as probes providing that the bacteriocin variant forms a chelated complex with the metal, and the bacteriocin-metal complex binds to pathogen, particularly gram positive bacteria and mycobacteria. Page 22, lines 6-18, emphasis added.

Therefore, Applicants submit that one of ordinary skill in the art would have no difficulty realizing that Applicants were in possession of the claimed subject matter when the application was filed. Accordingly, Applicants assert that claims 1-4, 7-9, 64, 66 and 67 are patentable under 35 U.S.C. § 112, first paragraph, and respectfully request removal of this rejection. The remarks set forth above would equally apply to claims 6 and 65 if the Examiner agrees that these claims are within the elected subject matter and would have been likewise rejected under § 112, first paragraph.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4, 7-9, 64, 66 and 67 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that, while being enabling for complexes comprising a bacteriocin and a transition metal, the specification does not reasonably provide enablement for complexes comprising bacteriocin variants and transition metals. This rejection is respectfully traversed.

As discussed above, the terms "fragments," "homologs," and "variants" of complexes of bacteriocins are well-known in the field and are specifically defined by Applicants. Thus, the terms would be easily understood by one of skill in the art and, given that understanding, one of ordinary skill in the art would clearly be enabled by the disclosure provided by the specification to formulate the claimed complexes.

Moreover, 35 U.S.C. § 112, first paragraph, reads as follows: *The specification shall* contain a written description of the invention, *and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same,* and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the enablement requirement is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the specification and the knowledge in the art. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1896 (Fed. Cir. 1991). The enablement requirement is met if the description enables any mode of making and using the claimed invention. *Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 20 USPQ2d 1300 (Fed. Cir. 1991). The Federal Circuit has

explained that the question of undue experimentation is not a single, simple factual determination, but rather, it is a conclusion that is reached by weighing many factual considerations. *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) (The key word is "undue," not "experimentation.").

In *In re Wands,* the Federal Circuit set forth eight factors to consider when determining whether a disclosure would require undue experimentation, they are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. The Federal Circuit has, on more than one occasion, cautioned that the *Wands* factors are illustrative and not mandatory and that all of the factors need not be reviewed when determining whether a disclosure is enabling. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), citing, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.,* 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), *cert. denied,* 502 U.S. 856 (1989).

Applying the *Wands* factors, the Examiner takes the position that the claimed invention is not enabling. The following discussion will demonstrate the errors in the Examiner's *Wands* factor analysis and why the claimed invention is legally enabling.

THE QUANTITY OF EXPERIMENTATION

The Examiner provides no commentary on this *Wands* factor. Applicants are interpreting the Examiner's silence on this factor to be an acknowledgement that the application is enabling in light of the specification.

THE AMOUNT OF DIRECTION OR GUIDANCE PRESENTED

The Examiner contends that while Applicants have provided general definitions of the terms in the specification, the application "does not disclose any examples, or any other guidance to guide those in the art to such variants." Applicants disagree.

As discussed above, the specification sets forth specific examples of fragments, homologs, and variants of complexes of bacteriocins that would be suitable in the claimed invention. For instance, acceptable homologs include homologs to nisin, which are generally

peptides whose nucleic acid sequence hybridizes to the nucleic acid sequence for nisin (SEQ ID NO:8) under stringent conditions, wherein such homologs would be expected to form similar metal chelates and bind to target pathogens with the same characteristics of the bacteriocins described herein. See page 10, lines 1-24 of the specification. Other acceptable homologs include bacteriocin homologs encoded by DNA sequences capable of hybridizing with the DNA sequences described herein, or sequences which code for the bacteriocin amino acid sequences disclosed herein using the degeneracy of the genetic code and coding for proteins having substantially the same activity. See page 11, lines 3-9 of the specification. Suitable fragments, homologs and variants include fusion proteins of any of the generally cationic peptides synthesized by bacteria, plants, mammals or insects having antimicrobial activity and forming complexes with transition or lanthanide metals, such as, diverse species of cationic membrane active peptides such as the non-lanthionine containing bacteriocins, defensins, cecropins, and magainins. See page 19, lines 1-13 of the specification. Suitable variants include engineered variants such as fusion proteins or constructs comprising the amino acid sequence of one or more bacteriocins such as a fusion protein comprising multiple copies of a bacteriocin, wherein a preferred bacteriocin for constructing a multimer of bacteriocins is nisin having spacer sequences comprising an amino acid sequence of between about 5 to about 25 amino acids, preferably between about 1 to about 10 amino acids, included between the C-terminus of one subunit of bacteriocin and the N-terminus of the next bacteriocin. See page 22, lines 6-18 of the specification.

Moreover, the Examiner himself cites Gasson et al., WO 96/16180 (hereinafter "Gasson"), in combination with three other references, as disclosing methods of making and using antibacterial variants of nisin, in support of his rejection of particular claims under § 103 as being obvious. Clearly then, making nisin and other bacteriocin variants is well within the knowledge of those skilled in the art and therefore the application is enabled and meets the written description requirements.

THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

The Examiner contends that while Applicants have provided general definitions of the terms in the specification, the application "does not disclose any examples, or any other guidance to guide those in the art to such variants." Applicants disagree for the reasons stated above.

THE NATURE OF THE INVENTION

The Examiner provides no commentary on this *Wands* factor. Applicants are interpreting the Examiner's silence on this factor to be an acknowledgement that the application is enabling in light of the nature of the invention.

THE STATE OF THE PRIOR ART

The Examiner provides no commentary on this *Wands* factor. Applicants are interpreting the Examiner's silence on this factor to be an acknowledgement that the application is enabling in light of the state of the prior art. Again, referring to the Gasson reference, it is clear that making nisin and other bacteriocin variants is well described in the art.

THE RELATIVE SKILL OF THOSE IN THE ART

The Examiner provides no commentary on this *Wands* factor. Applicants are interpreting the Examiner's silence on this factor to be an acknowledgement that the application is enabling to persons skilled in the art. *See,* MPEP § 2164.05(b) for a discussion of the requirements for the *Wands* factor relating to the relative skill of those in the art. Again, referring to the Gasson reference, it is clear that making nisin and other bacteriocin variants is well within the knowledge of those skilled in the art.

THE PREDICTABILITY OR UNPREDICTABILITY OF THE ART

The Examiner contends that the art surrounding the variation of bacteriocin composition is unpredictable citing Bowie et al. *Science* 247:1306-1310 (1990).

MPEP § 2164.03 explains that the "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. MPEP § 2164.03, p. 2100-182, 1st col., 2nd ¶. In other words, if one skilled in the art

can readily anticipate the effect of a change within the subject matter (such as a newly found species) to which the claimed invention pertains, then there is predictability in the art. *Id.* By contrast, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is a lack of predictability in the art. *Id.* With respect to the amount of disclosure required in an unpredictable art, the MPEP notes that even in unpredictable arts, a disclosure of every operable species is not required, but more than one will usually be necessary. MPEP § 2164.03, p. 2100-182, 2nd col., 2nd ¶.

Applicants disagree that complexes comprising bacteriocin fragments, homologs, or variants are not enabled in the specification as set forth above with respect to the amount of guidance presented in the specification. Further, Applicants disagree that making bacteriocin fragments, homologs, or variants is an unpredictable art. Bowie sets forth a number of factors that dictate the effects of altering amino acid sequences. For instance, Bowie states that (1) "most" of the structural information when performing substitution at surface and buried positions is carried by the residues that are solvent inaccessible; (2) in general "only hydrophobic or neutral" core residues are tolerated at buried sites in proteins; (3) the acceptable core sequences are composed "almost exclusively" of Ala, Oys, Thr, Val, Ile, Leu, Met, and Phe; (4) many surface sites can tolerate a wide variety of side chains, including hydrophilic and hydrophobic residues; and (5) many surface sites can accept hydrophobic residues individually, but the surface sites as a whole can probably tolerate only a moderate number of hydrophobic side chains. Moreover, Bowie is concerned with implications of structure prediction for synthesizing *new* proteins and the difficulties of such. Thus, Bowie sets forth factors to be considered when synthesizing new amino acid structures. Applicants' claims, however, are *not* concerned with synthesizing new amino acid structures, but rather are directed to known bacteriocin fragments, and homologs, and variants thereof. In general, Bowie does not support the Examiner's position that the art is unpredictable, but in fact teaches the opposite, if anything, by setting forth guidelines in the art of amino acid manipulation.

THE BREADTH OF THE CLAIMS

The Examiner contends that the claims read expansively on complexes comprising any fragment, homolog, or variant of any bacteriocin.

Turning to the MPEP for guidance, it is explained in MPEP § 2164.08 that claims cannot be rejected as overly broad for not reciting limitations that are known to one or ordinary skill in the art. MPEP § 2164.08 citing *W.L. Gore & Assoc., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1558, 220 USPQ 303, 316-317 (Fed. Cir. 1983); *In re Johnson,* 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). To illustrate the importance of this requirement, the following statement is quoted in the MPEP from *In re Goffe,* 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. MPEP § 2164.08, p. 2100-191, 2nd col., 1st ¶.

It is further explained in the MPEP that when analyzing the enabling scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation consistent with the specification. MPEP § 2164.08, p. 2100-191, 2nd col., 2nd ¶. Accordingly, it is unreasonable for the present claims to be limited to the specific bacteriocin fragments, homologs, or variant thereof disclosed in the specification. Applicants are entitled to broader protection in light of the specification and the knowledge in the art.

Accordingly, Applicants assert that claims 1-4, 7-9, 64, 66 and 67 are patentable under 35 U.S.C. § 112, first paragraph, and respectfully request removal of this rejection. The remarks set forth above would equally apply to claims 6 and 65 if the Examiner agrees that these claims are within the elected subject matter and would have been likewise rejected under § 112, first paragraph.

REJECTION UNDER 35 U.S.C. §102(b) OVER POMMER

Claims 1-4 and 7 stand rejected under 35 U.S.C. §102(b) as being anticipated by Pommer. According to the Examiner, Pommer discloses a bacteriocin that binds to zinc, nickel or cobalt forming a complex and that these complexes bind to and enter bacterium, including E. coli.

Claim 1 has been amended to recite that the complexes are synthesized or formed *in situ* in a sample to be tested, thereby distinguishing the invention over complexes such as those

described by Pommer, that occur in nature. Applicants respectfully point out that for a reference to be §102 art, the reference must teach the **same** invention. One of skill in the art would not assert that a naturally occurring bacteriocin bound to a transition metal is the "same" as a bacteriocin-metal complex that is synthesized or that is formed *in situ*, as is required for a proper §102 rejection.

In fact, Pommer states that the role of the metal ion was **unknown**, but was suggested to be either structural and/or catalytic. Moreover, according to Pommer, the "present data demonstrate that the transition metal bound in the HNH motif of colicin endonucleases is not essential for the random hydrolysis of plasmid DNA substrates and indeed may even inhibit this activity." Page 27155 of Pommer. Further yet, Pommer states that removal of the metal ion from the DNase may be required for the penetration of the DNase into a bacterial cell. See page 27159 of Pommer. Thus, Pommer teaches away from synthetically creating bacteriocins with transition metals to form a complex that finds utility in the detection of biological analytes.

The present invention is further distinguishable from Pommer in that a specific advantage of the present invention is the ability of the synthesized or *in situ*-formed complex to detect viable cells. The bacteriocin complexes bind to and form pore structures through the bacterial membrane thereby serving as vital stains to indicate the presence of viable bacteria. See page 14, lines 3-8 of the specification. Pommer only discusses that the naturally occurring complexes bind to and enter bacterium. There is nothing in Pommer to suggest that synthetic complexes would have any usefulness in binding to and forming pore structures, which serves as a vital stain.

Therefore, since Pommer does not teach synthesized or *in situ*-formed complexes, Pommer cannot be said to anticipate the present invention. The remarks set forth above would equally apply to claim 6 if the Examiner agrees that this claim is within the elected subject matter and would have been likewise rejected under § 102(b). Accordingly, the rejection on this basis is traversed and withdrawal thereof is respectfully requested.

REJECTION UNDER 35 U.S.C. §103(a), OVER SIDDIGI IN VIEW OF OLSTEIN AND TIMMER

Claims 1-4, 7-9 and 64 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Siddigi et al., U.S. Patent No. 5,541,113 (hereinafter "Siddigi") in view of Olstein et al., U.S.

Patent No. 5,750,357 (hereinafter "Olstein") and Timmer et al., EP 0659068 (hereinafter "Timmer"). According to the Examiner, Siddigi teaches methods for detecting analytes such as bacteria comprising attaching a transition metal label to a ligand and measuring the presence of the label to determine the presence of an analyte in a sample; Olstein teaches the use of chemically labeled antibiotics as ligands for the detection of pathogenic microorganisms; and Timmer teaches that lantibiotics including nisin are a well-known class of antibiotics. The Examiner concludes that because Timmer teaches that nisin is an antibiotic peptide and Olstein teaches that antibiotic peptides are useful ligands to bacteria, it would have been obvious to use nisin in the method described in Siddigi. Applicants respectfully disagree.

First, the Examiner acknowledges that Siddigi does **not** teach or suggest the use of bacteriocins as acceptable ligands, and therefore does not teach or suggest the presently claimed complexes comprising a bacteriocin and a transition metal. Moreover, Siddigi only covers a method for detecting an analyte by adding a label, an ECL cofactor such as an amine, and an analyte to an aqueous solution and detecting the analyte. Nowhere in the present application do the methods of detecting an analyte require the use of an ECL cofactor such as an amine, which is fundamentally different from what is taught in Siddigi. Thus, the presently claimed complexes comprising a bacteriocin and a transition metal and the methods of their use is not taught or suggested by Siddigi. Further, the deficiencies in the primary Siddigi reference are not remedied by the teachings of the secondary Olstein and Timmer references.

The Examiner further acknowledges that Olstein does **not** teach or suggest the use of bacteriocins, lantibiotics, or nisin as an acceptable antibiotic ligand, and therefore does not teach or suggest the presently claimed complex comprising a bacteriocin and a transition metal. Olstein also does **not** teach or suggest the use of transition metals as a detectable label, but rather teaches the use of avidin as the label. Olstein is further distinguishable from the present invention since Olstein covers a synthetic copolymer having repeating units, wherein one group of monomeric units comprises a binding agent such as an antibiotic ligand and a second group of monomeric units comprises a detectable label or a binding site for a detectable label. Such a synthetic copolymer is completely structurally unrelated to the presently claimed complexes comprising a bacteriocin and a transition metal.

There would be no motivation to combine the teachings of Olstein with the teachings of Siddigi. The compounds used to detect bacteria in these references are completely structurally unrelated. More importantly, even if the two references were combined, one skilled in the art would not arrive at present invention - synthetic or *in situ*-formed complexes comprising a bacteriocin and a transition metal. The additional combination of Timmer does not cure the fundamental defects in Siddigi and Olstein and does not provide any motivation for the combination of the three references.

Timmer covers a method of removing plaque in the oral cavity by using mouth care products including specific bactericine compounds such as lantibiotics. While Timmer does state that lantibiotics have antibiotic activity and include nisin, Timmer also states that nisin was, at the time, used as a food preservative. Based on this alone, there is no motivation to combine the teaching of Olstein, which relates to a method of analyte detection with the teachings of Timmer, which relates to mouth-care products.

Even if Timmer and Olstein were combined, at best, one would achieve a synthetic copolymer having repeating units, wherein one group of monomeric units comprises a binding agent such as an antibiotic ligand including nisin and a second group of monomeric units comprises a detectable label or a binding site for a detectable label. Again, such a synthetic copolymer is completely structurally unrelated to the presently claimed complexes comprising a bacteriocin and a transition metal.

Although the claims are not rejected over Meyer et al. *Arch Microbiol* 167:67-77 (1997) (hereinafter "Meyer"), the Examine notes that Meyer teaches that nisin and the other lantibiotics bind to the membranes of target cells, thus demonstrating that these peptides are pathogen ligands. Meyers does not teach or disclose the claimed complexes comprising a bacteriocin and a transition metal and the methods of their use. Again, this additional reference does not cure the deficiencies in the primary Siddigi reference or the deficiencies in the other references. Thus, even if Meyer was cited against the claims in combination with the other references, one skilled in the art would not arrive at the claimed invention.

Accordingly, Applicants assert that claims 1-4, 7-9 and 64 are patentable under 35 U.S.C. §103(a), and respectfully request removal of this rejection. The remarks set forth above would

equally apply to claims 6 and 65 if the Examiner agrees that these claims are within the elected subject matter and would have been likewise rejected under § 103(a).

REJECTION UNDER 35 U.S.C. §103(a), OVER SIDDIGI IN VIEW OF OLSTEIN, TIMMER AND GASSON

Claims 66 and 67 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Siddigi in view of Olstein and Timmer as applied to claims 1-4, 7-9 and 64 above, and further in view of Gasson. According to the Examiner, Gasson teaches how to make and use antibacterial variants of nisin, wherein such variants maintain antibacterial activity, and thus it would have been obvious to make such variants and use them in the method described in Siddigi.

The same deficiencies in Siddigi, Olstein, and Timmer discussed above are equally applicable here. In addition, there is no motivation for a skilled artisan to combine the teachings of Siddigi, which pertains to using an amine and a label to detect an analyte, with that of Olstein, which pertains to using synthetic copolymers to detect an analyte, Timmer, which pertains to mouth-care products, and Gasson, which pertains to methods of producing nisin variants. The additional disclosure in Gasson does not cure the deficiencies in the other three references discussed above. Thus, even if Siddigi was combined with Olstein, Timmer, and Gasson, the skilled artisan would not arrive at the claimed invention for reasons discussed above.

Accordingly, Applicants assert that amended claims 66 and 67 are patentable under 35 U.S.C. §103(a), and respectfully request removal of this rejection. The remarks set forth above would equally apply to claim 65 if the Examiner agrees that this claim is within the elected subject matter and would have been likewise rejected under 35 U.S.C. §103(a).

OTHER REFERENCE NOTED

Isacsson et al., *Analytica Chimica Acta* 68:339-62 (1974) is cited to further show the state of the art with respect to the use of luminol, its oxidants and transition metal catalyst in detection assays.

Applicants have reviewed this reference and agree with the Examiner's implicit finding that the reference does not disclose or suggest the presently claimed invention.

SUMMARY

The above arguments, amendment to claim 1, and amendments to the specification are submitted for the purpose of facilitating allowance of the claims and a sincere effort has been made to place this application in condition for allowance. An early notice of allowance is earnestly requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 330-4916.

Respectfully submitted,

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